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Glutamic acid decarboxylase (GAD) antibodies in epilepsy: Diagnostic yield and therapeutic implications

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ABSTRACT

Purpose: The aetiology of adult onset epilepsy remains unascertained in a significant proportion of patients. Antibodies directed against neuronal antigens have been suggested to have a potential pathogenic role in some cases of epilepsy. We describe a series of patients with adult onset epilepsy in whom antibodies to glutamic acid decarboxylase (GAD Abs) have been identified.
Methods: All patients attending a regional epilepsy service with unexplained adult onset epilepsy' were tested for the presence of GAD Abs. Those with high serum titres underwent CSF analysis, and were offered additional treatment with immunotherapy. Those who underwent immunotherapy were monitored by monthly review. Clinical details and response to treatment was collated by review of notes.
Results: Of 112 patients tested, high serum titres were found in 6 (5.4%) patients. These patients had clinical and electroencephalographic evidence of focal epilepsy. CSF analysis revealed oligoclonal bands and intrathecal GAD Abs in all patients. Five patients received immunotherapy. No improvement in seizures was observed in any. One patient with equivocal MRI evidence of hippocampal sclerosis and concordant video EEG and PET scan, achieved 12 months seizure freedom following temporal lobectomy.
Conclusions: The relevance of GAD Abs to epilepsy remains uncertain. Our experience does not support the routine use of immunotherapy in patients with epilepsy and GAD Abs. Larger studies enrolling greater numbers of patients are required to identify sufficient numbers of patients for controlled treatment trials.

1. Introduction

A significant number of patients develop epilepsy in adult life despite identification of epileptogenic abnormalities with brain imaging techniques in only a proportion.[1] A large number of patients with refractory epilepsy also have no identifiable structural brain abnormalities.[2] In recent years, a number of authors have reported serum autoantibodies in patients with epilepsy directed against neuronal cell surface antigens such as the voltage gated potassium channel (VGKC) complex and the *N*-methyl-D-aspartate (NMDA) glutamate receptor, as well as intracellular antigens such as glutamic acid decarboxylase (GAD).[3–7] Whilst these antibodies have mainly been identified in patients with the clinical syndrome of limbic encephalitis (LE), characterised by amnesia, encephalopathy or change in affect and seizures, often in association with brain imaging abnormalities,[8–10] they are also found in patients with seizures alone.[4,11] This raises the possibility of an autoimmune aetiology in some patients with otherwise unexplained epilepsy.

Favourable responses to immunotherapy have been observed in patients with other neurological conditions, particularly where associated with antibodies directed against neuronal cell surface antigens.[12–14] Immunotherapy may have a role in the treatment of patients with epilepsy, particularly when autoantibodies directed against neuronal cell surface antigens are found.[9,15]

GAD is the principal enzyme that catalyses the decarboxylation of the neurotransmitter glutamic acid to gamma-aminotobutyric acid (GABA). Antibodies directed against GAD (GAD Abs) have been found in patients with a number of neurological conditions including stiff person syndrome, cerebellar ataxia, limbic encephalitis, myoclonus and in patients with epilepsy alone.[16] Some

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authors noted a high prevalence of epilepsy in patients with stiff person syndrome and suggested a shared aetiology in such cases.[6,17] In patients with epilepsy and GAD Abs the use of immunotherapy has been attempted, with beneficial effect observed in some cases.[7,18] In this setting, the presence of intrathecal GAD Abs has been suggested as evidence of pathogenicity.[7]

Since January 2010, we have tested all adult patients attending our epilepsy service with 'unexplained adult onset epilepsy' for the presence of serum GAD Abs, VGKC-complex antibodies and NMDA receptor antibodies. We have previously reported the diagnostic yield for VGKC complex antibody testing and response to immunotherapy.[5] We describe a cohort of patients with 'unexplained adult onset epilepsy' in whom GAD Abs were detected.

2. Methods

We reviewed the medical notes up to January 2013 of patients with 'unexplained adult onset epilepsy' seen between January 2010 and December 2011 in tertiary epilepsy clinics in two hospitals in Greater Manchester, UK, who had been tested for the presence of serum GAD Abs. 'Unexplained adult onset epilepsy' was defined as focal or unclassified epilepsy with onset in adult life with no history of antecedent cerebral insults and no epileptogenic lesions identified on MRI scanning using appropriate imaging protocols. Patients with clearly defined idiopathic generalised epilepsy syndromes, symptomatic epilepsies and patients with the either the clinical syndrome of LE or MRI evidence of inflammation were not included.

All sera were tested using the clinical service at the neuroimmunology laboratory at the University of Oxford using the Ria-RSR (radioimmunoassay) GADAb assay (RSR Ltd, Cardiff, UK) prior to September 2011 and the Elisa-RSR (ELISA) GADAb assay (RSR Ltd, Cardiff, UK) after this date. Samples were sent to the laboratory over the study period, and not tested as a single batch. A positive result was defined by the detection of GAD Abs at any concentration within the tested sera. We then categorised positive results from the Ria-RSR assay as either 'low positive' (1–1000 u/mL) or 'high positive' (>1000 u/mL). This categorisation was based on previous local experience and other studies which have demonstrated a similar prevalence of low positive GAD Ab titres in both epilepsy and control groups.[3,7] We have assumed therefore that the presence of GAD Abs at titres <1000 u/mL are not of clinical significance in this setting. Due to the different methodology used with the Elisa-RSR assay, results are not directly comparable with the Ria-RSR assay results and we defined a different cut off value for 'low' and 'high' positive results (5–50 000 U/mL and >50 000 U/mL, respectively).

As well as testing for GAD Abs, patients meeting the same inclusion criteria were also tested for VGKC complex antibodies and NMDA receptor antibodies. These results are not discussed further in this paper. Testing for other autoantibodies such as GABA-b and AMPA was not performed as these assays were not clinically available on a routine basis during the study period and because previous studies had focussed on VGKC complex, NMDA receptor and GAD Abs in patients with epilepsy.[3]

Patients found to have high positive GAD Ab titres were investigated further with lumbar puncture and cerebrospinal fluid (CSF) analysis as part of routine clinical evaluation in an effort to define the pathogenic relevance of the detected antibodies. These patients were offered treatment with immunotherapy in addition to standard treatment at the discretion of the treating physician.

In patients with high positive GAD Ab titres, demographic information was collected and clinical details, investigation results and response to treatment was observed and documented at monthly review by one of the authors and collated retrospectively by review of clinical records.

3. Results

During the study period 112 patients were tested for the presence of serum GAD Abs. 14 (12.5%) were found to be positive. Of these 6 (5.4%) patients had high positive serum GAD Ab titres. The clinical characteristics of these patients are summarised in Table 1. Eight remaining patients (7.1%) had low positive GAD Ab titres. These patients were not retested and will not be discussed further in this paper.

All patients with high positive GAD Ab titres were female, with a mean age of 35 years (range 20–44). Four of the six patients had other autoimmune diseases, including one patient with type 1 diabetes.

All six patients had focal seizures with clinical localisation of the seizure focus to the temporal lobe in five patients. In one remaining patient the clinical localisation of the seizure focus was uncertain. Five patients also experienced generalised tonic clonic seizures at some point since the onset of epilepsy. The median time from onset of epilepsy to antibody testing was 9.5 years (range 1.25–23) and all patients were already receiving appropriate antiepileptic drug (AED) treatment.

All patients had lumbar puncture following identification of high positive serum GAD Ab titres. Biochemical and microbiological parameters were within normal limits apart from a slightly raised CSF protein in one patient (Patient C, 0.52 g/L). GAD Abs were detected in the CSF of all patients. Oligoclonal bands were present in the CSF and unmatched in the serum in all patients. One patient also had additional matching bands in the CSF and serum.

All of the patients had epilepsy protocol MRI imaging of the brain prior to antibody testing. In all cases this was reported as normal by a consultant neuroradiologist. In Patient A, subsequent review during follow up, and further imaging with FDG-PET as part of an epilepsy surgery workup revealed left mesial temporal hypometabolism suggestive of mesial temporal sclerosis. We have not excluded this patient from the analysis as at the point of entry into the study the inclusion criteria were met. Extra-cranial imaging was not performed in any patient.

Routine and prolonged EEG recordings captured focal slow waves, and sharp and slow wave complexes in all patients. Video telemetry (VT) evaluation was performed in all patients. Seizure semiology, interictal and ictal EEG patterns and seizure classifications are summarised in Table 2. Typical attacks were recorded during VT in three of six patients, all of whom were confirmed to have focal epilepsy. The semiology included features suggestive of temporal lobe onset, but in two of the three patients additional seizures, likely to be of extra-temporal origin were also captured. In Patient A, all seizures captured were of left mesial temporal origin. This patient was subsequently entered into the epilepsy surgery programme. No seizures were captured in three patients, but focal interictal abnormalities were recorded in all.

At the point of antibody testing, all six patients were experiencing ongoing seizures despite appropriate AED therapy. Additional immunotherapy was received by five of the six patients with high positive serum GAD Ab titres, GAD Abs detected in the CSF and oligoclonal bands detected in the CSF unmatched in serum, with the assumption that epilepsy in these patients may be of an autoimmune aetiology and with the objective of improving seizure control. Of these five patients, four received intravenous methylprednisolone (IVMP) followed by oral prednisolone. IVMP was administered at a dose of 1 g per day for 3 days. Oral prednisolone was commenced at 1 mg/kg/day and tapered at the discretion of the treating physician. All patients had stopped prednisolone by 12 weeks.

Table 1
Clinical characteristics of patients with epilepsy and high positive (>1000 u/mL) GAD Ab titres.

	Age, Sex	Seizure type and epilepsy syndrome	Duration of epilepsy at antibody testing	AED's used prior to immunotherapy	Seizure frequency at time of antibody testing	Other autoimmune disorders	Serum anti-GAD titre (u/mL)	Cerebrospinal fluid analysis	CSF anti-GAD titre (μ/mL)	MRI brain	Immunotherapy	Response to immunotherapy
Patient A	41, F	FS and GTCS Focal Epilepsy (temporal lobe)	14 years	Carbamazepine, Lamotrigine, Levetiracetam, Pregabalin	1–4 FS per month	Rheumatoid arthritis, hypo-thyroidism	>1000	Normal cell count, protein, glucose. CSF OCBs present unmatched in serum	110	Reported as normal at time of entry into study	IVMP then oral prednisolone (on MTX for RA)	No improvement. Entered into epilepsy surgery programme
Patient B	41, F	FS Focal Epilepsy (temporal lobe)	15 months	Lamotrigine, Levetriacetam, Zonisamide	1–2 FS per month	Type 1 Diabetes, Coeliac Disease	>1000	Normal cell count, protein, glucose. CSF OCBs present unmatched in serum	66	Normal	IVIG for 3 months, azathioprine	No FS for 11 months following IVIG, but subsequent persistent recurrence despite azathioprine. Patient also developed optic neuritis and transverse myelitis.
Patient C	24, F	FS and GTCS Focal Epilepsy (temporal lobe)	5 years	Carbamazepine, Oxcarbazepine, Levetiracetam	4–5 FS per week	None	>1000	Normal cell count and glucose. Protein 0.52 g/L. CSF OCBs present unmatched in serum	>200	Normal	IVMP then oral prednisolone and azathioprine	No improvement. Hepatotoxicity from Azathioprine
Patient D	44, F	FS and GTCS Focal Epilepsy (temporal lobe)	14 years	Lamotrigine, Levetiracetam, Oxcarbazepine	1–2 FS per week	Hypo-thyroidism	>50 000*	Normal cell count, protein, glucose. CSF OCBs present unmatched in serum	18 596*	Normal	IVMP then oral prednisolone	No improvement in seizure frequency. Cerebellar ataxia developed during follow up and improved with immunotherapy
Patient E	20, F	FS and GTCS Focal Epilepsy (clinical focus uncertain)	2 years	Carbazmazepine, Lamotrigine, Clobazam	5–10 FS per week	Coeliac disease, pernicious anaemia	>1000	Normal cell count, protein, glucose. CSF OCBs present unmatched in serum	>200	Normal	IVMP, Prednisolone, IVIG, PEx. Azathioprine	No improvement.
Patient F	42, F	FS and GTCS Focal Epilepsy (temporal lobe)	23 years	Carbamazepine, Levetiracetam	3–4 FS per week	None	>1000	Normal cell count, protein, glucose. CSF OCBs present unmatched in serum with additional matched bands found	>200	Normal	None	n/a

Abbreviations: AED – antiepileptic drug; FS – focal seizures; GTCS – generalised tonic clonic seizures; CSF – cerebrospinal fluid; OCBs – oligoclonal bands; IVMP – intravenous methyl prednisolone; IVIG – intravenous immunoglobulin; PEx – plasma exchange; MTX – methotrexate; RA – rheumatoid arthritis.

* Patient D was tested using the Elisa-RSR assay with different reference ranges defined. The other patients were tested using the Ria-RSR assay (see Section 2).

Table 2
Video EEG evaluation of six patients with refractory epilepsy and anti-GAD antibodies.

	Interictal	Semiology	Ictal	Seizure classification
Patient A	Left anterior temporal sharp waves	De ja vu, loss of awareness, oro-facial and upper limb automatism, post ictal aphasia	Left anterior temporal theta	Left mesial temporal lobe epilepsy
Patient B	Frequent left anterior temporal sharp waves, occasional right temporal sharp activity	1. De ja vu, loss of awareness (x2) 2. No aura, tonic left arm posturing (x2)	1. Left anterior temporal rhythmic delta 2. Right frontotemporal sharp waves	Multifocal epilepsy
Patient C	Infrequent low amplitude right fronto-temporal sharp waves	1. No aura, oro-facial automatisms (x2) 2. No aura, asymmetric tonic posturing arms, left hand clonic (x1)	1. No scalp EEG changes 2. Right frontocentral (F4/C4) 6 Hz	Multifocal epilepsy
Patient D	Infrequent left anterior temporal (F7) sharp waves	No events captured	n/a	n/a
Patient E	Slowing of background Focal sharp waves right temporal region	No events captured	n/a	n/a
Patient F	Left anterior temporal sharp waves	No events captured	n/a	n/a

Patient E received intravenous immunoglobulin (IVIg), plasma exchange and azathioprine in addition to corticosteroids. Patient C also received azathioprine after an induction phase with corticosteroids. Corticosteroids were avoided in Patient B who had type 1 diabetes. In this patient, a period of induction with IVIG followed by azathioprine were used as an alternative. IVIG was administered on a monthly basis at a dose of 2 g/kg for 3 months. Patient A continued on long term treatment with methotrexate throughout the study period as part of treatment for coexisting rheumatoid arthritis.

No sustained improvement in seizure frequency was seen in any patients receiving immunotherapy during the follow up period and treatment reverted back to AEDs alone in all patients apart from Patient B. This patient developed optic neuritis, and subsequently transverse myelitis during the study period and also had a background of type 1 diabetes and coeliac disease. Azathioprine was continued in this patient with the presumed diagnosis of an autoimmune inflammatory brain disorder. Patient D developed cerebellar ataxia during follow up without any associated change in seizure frequency. This patient experienced improvements in ataxia with immunotherapy but no change in seizure frequency.

After the unsuccessful trial of immunotherapy and further investigation after VT with FDG-PET, Patient A was entered into the epilepsy surgery programme and underwent standard left anterior temporal lobe resection. Post operatively the patient was seizure free for 10 months after which occasional focal seizures without loss of awareness occurred, up to 18 months of follow up post operatively. Prior to surgery the patient had experienced focal seizures with loss of awareness and generalised tonic clonic seizures. Histological analysis of the resected specimen showed end folium sclerosis, with no evidence of active inflammation. GAD Abs have persisted in the serum at high titres following surgery.

4. Discussion

We detected high serum titres (>1000 u/mL) of GAD Abs in 5.4% (6/112) of patients with otherwise unexplained adult onset focal epilepsy. These patients were also tested for antibodies directed against the VGKC complex and to NMDA receptors, which were not detected. CSF analysis showed the presence of intrathecal GAD Abs as well as unmatched CSF oligoclonal bands in all patients. Four of these patients had other autoimmune disorders. Immunotherapy did not result in sustained improvement in seizure control in any of our patients.

Exact comparison of prevalence data with other studies is difficult due to the use of differing arbitrary cut-off values for high and low levels of positivity and the fact that our study only examined patients with focal epilepsies, which appear to have a higher prevalence of antibody positivity as compared to those with generalised epilepsy syndromes.[6] Liimatainen et al. found 2.8% of patients they tested with refractory focal epilepsy were positive for GAD Ab in titres (>1000 u/mL).[7] In their study, Peltola et al. found 3.9% of patients in a subgroup with focal epilepsy had GAD Ab titres >1000 u/mL.[6] Our study did not have a control group. Other studies have found only low prevalence of GAD Abs at any level in healthy controls (0–1.5%).[4,6,7]

Patient A had an FDG-PET scan after VT had demonstrated electrographic seizures arising from the left temporal lobe, which demonstrated hypometabolism in the left temporal lobe. Retrospective review of the MRI scan performed prior to entry into the study, which was reported as normal, was suggestive of hippocampal atrophy. This patient became seizure free following epilepsy surgery, although focal seizures without loss of awareness have since recurred. Based on this, we feel that epilepsy surgery should not be ruled out in patients with refractory temporal lobe epilepsy based on the presence of GAD Abs alone.

One patient (Patient D) had cerebellar ataxia which responded well to immunotherapy whilst the seizure control did not. Whilst the coexistence of epilepsy and cerebellar ataxia in this patient may simply be a chance association, this finding is of interest and may suggest different pathological mechanisms for each disorder given the differential response to immunotherapy. Another patient with co-existing type 1 diabetes and coeliac disease went on to develop optic neuritis and subsequently transverse myelitis, and remains on long term immunosuppression for a presumed autoimmune inflammatory brain disorder, perhaps indicating that GAD Abs in this patient are simply an epiphenomenon of another autoimmune process.

None of our patients had a sustained response to immunotherapy and as such our experience does not support the use of immunotherapy in patients with unexplained adult onset focal epilepsy in whom serum or CSF GAD Abs are identified. Treatment responses in patients with other neurological syndromes associated with GAD Ab are variable and there have been reports of successful outcomes in stiff person syndrome,[19] limbic encephalitis[8] and epilepsy.[7,11]

The presence of oligoclonal bands within the CSF of patients with LE is thought to support the notion that an autoimmune mechanism underlies the pathogenesis of the syndrome.[20] In patients with epilepsy alone, it has been suggested that the presence of intrathecal GAD Ab is of particular importance in identifying patients who may respond to immunosuppression.[7] The lack of improvement seen in our cohort of patients with epilepsy who received immunosuppression, all of whom had the presence intrathecal GAD Ab and CSF oligoclonal bands unmatched in serum, does not support this hypothesis.

The relevance of GAD antibodies in epilepsy remains uncertain. In common with onconeural antibodies, and in contrast to the cell surface antibodies such as those directed against the VGKC complex or the NMDA receptor, GAD Abs are directed against an intracellular antigen. The proposed pathogenic mechanisms of neurological disease in patients with antibodies directed against intracellular proteins is not clear, although may be mediated by cytotoxic T cells, leading to inflammation.[13,21] Inflammatory changes were not demonstrated in histological specimens from Patient A, who underwent left anterior temporal lobe resection. Given that this patient had been experiencing seizures for 14 years prior to antibody testing it is possible that any active autoimmune process may have "burnt out". This could be consistent with the hypothesis that an acute autoimmune illness with hippocampal inflammation could lead to development of hippocampal sclerosis and subsequent chronic temporal lobe epilepsy[14,22,23] and might explain the poor response to immunotherapy in the chronic phase. In contrast to this, a response to immunotherapy has been observed in patients with epilepsy and VGKC-complex antibodies up to 2 years after onset of seizures[5] possibly indicating different pathogenic processes involved in the generation of epilepsy with different autoantibodies.

The possibility of GAD Abs being generated as an epiphenomenon of recurrent seizures also exists, although Brenner and colleagues have contended that the similar prevalence of GAD Abs found in newly diagnosed and chronic epilepsy indicates that GAD Ab are not caused by recurrent seizures.[4] One patient in our series (patient B) went on to develop a more widespread CNS inflammatory disorder, with optic neuritis and subsequently transverse myelitis, in whom it would be reasonable to regard the presence of GAD Ab as an epiphenomenon, acting as a marker for an immune mediated process, rather than being a pathogenic antibody. Other studies have demonstrated the co-existence of GAD Abs and autoantibodies directed against neuronal surface antigens in patients with LE, the latter of which appears more likely to be pathogenic.[11,24]

Due to the retrospective design and observational method employed, our study has a number of limitations. Antibody testing and subsequent treatment was carried out in a clinical and pragmatic way. The immunotherapy regimen was determined at the discretion of the treating physician, and more potent therapies such as cyclophosphamide were not used. We did not include a control population and patients were not screened extensively for co-existing neuronal autoantibodies. The patients we identified with high positive GAD Ab titres also had a high prevalence of other autoimmune disease, with 1 patient having type 1 diabetes. As the presence of GAD Abs may be a manifestation of other autoimmune disease, this factor may have contributed to the poor response of epilepsy to immunotherapy observed in our cohort, despite the apparent evidence of a CNS based inflammatory process as suggested by the presence of intrathecal GAD Abs and oligoclonal bands within the CSF unmatched in serum.

Systematic testing of large cohorts of epilepsy patients will be required to identify sufficient patients with autoantibodies for further analysis and controlled trials of immunosuppressive treatment, before any firm conclusions regarding the relevance of autoimmunity in patients with epilepsy and GAD Abs.

Conflicts of interests

None declared.

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